



170037
62000

PCT/EP 00 / 065 45

REC'D 15 AUG 2000



WIPC

PCT

INVESTOR IN PEOPLE

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

EP 00 / 065 45

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

EP 00 / 065 45

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

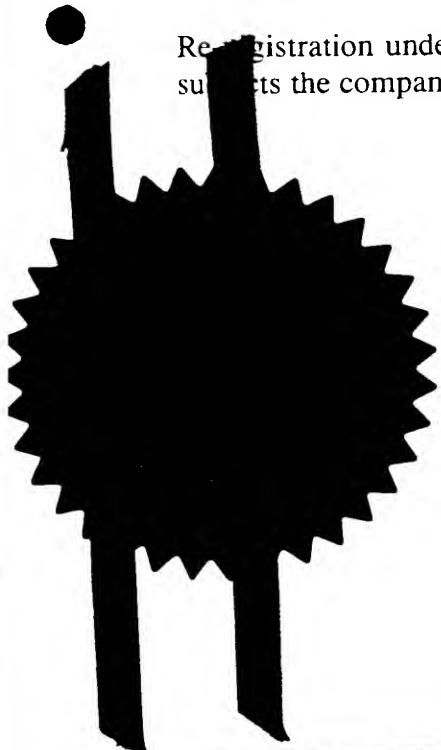
In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

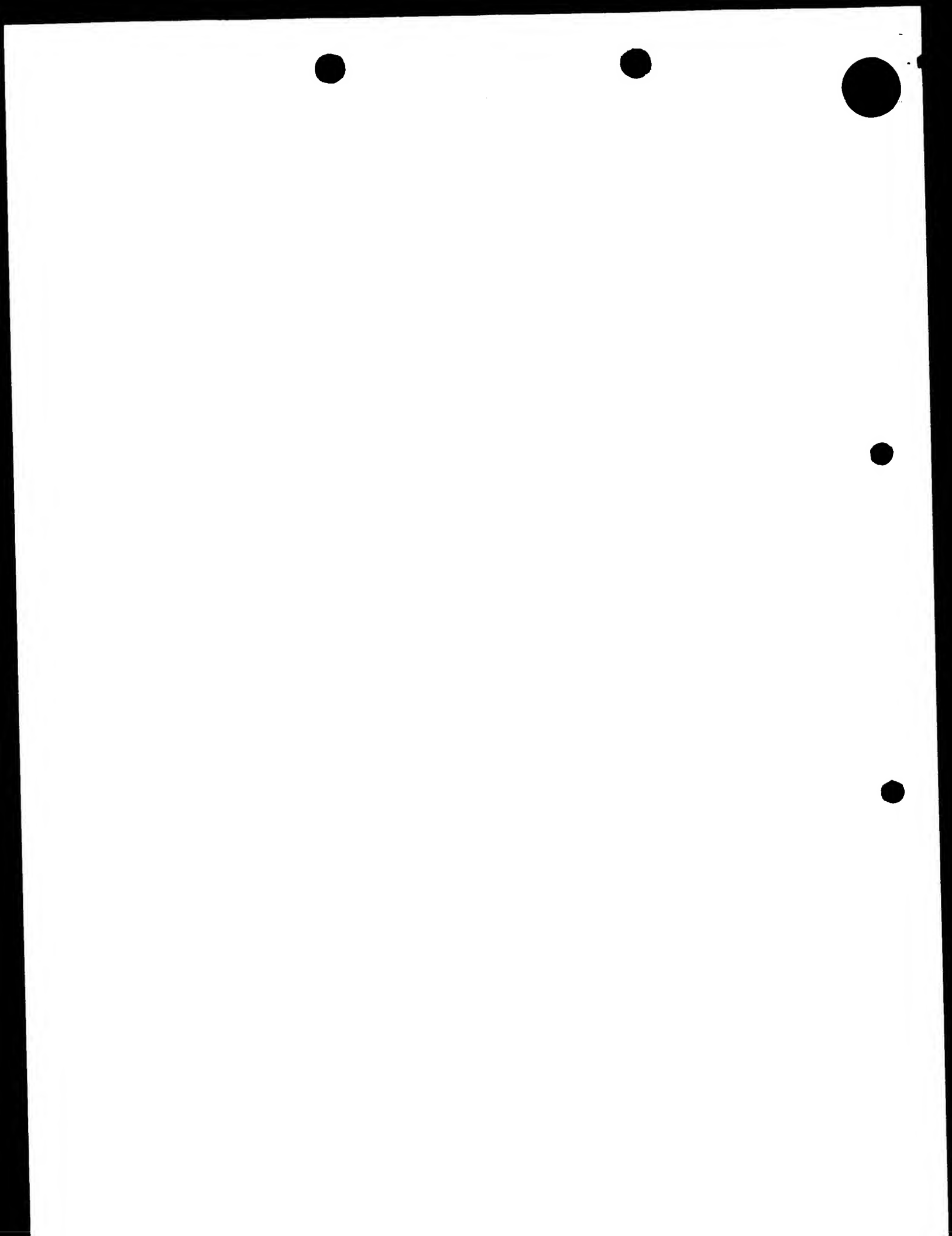
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Andrew

Dated 25 May 2000





Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form.)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference P77426 GCW CMK

2. Patent application number

(The Patent Office will fill in this part)

18 JUL 1999

9916882.5

3. Full name, address and postcode of the or of each applicant (underline all surnames)

PHARMACIA & UPJOHN SPA
VIA ROBERT KOCH 1,2
20152 MILAN

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

ITALY



4. Title of the invention

ANTITUMOR SYNERGISTIC COMPOSITION

5. Name of your agent (if you have one)

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LN

Patents ADP number (if you know it)

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer Yes or No)

YES

a. any applicant named in part 3 is not an inventor, or
b. there is an inventor who is not named as an applicant, or
c. any named applicant is a corporate body.
See note 4.

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	4
Claim(s)	2
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*) 2 x 5

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(*please specify*)

11 I/We request the grant of a patent on the basis of this application

Signature

J.H. Keen

Date 19 July 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS C.M. KEEN
0171 405 3292

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

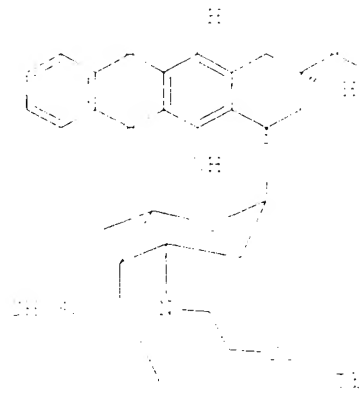
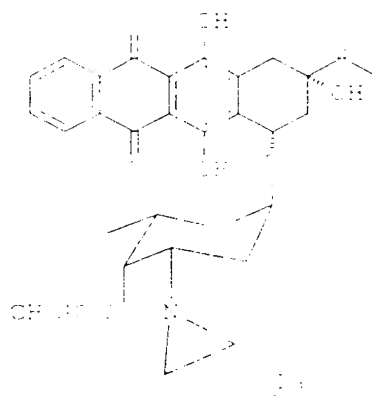
- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue of a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered "Yes" Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

Antitumor Synergistic Composition

The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and an antiviral compound, having a synergistic antitumor antineoplastic effect.

The present invention is viewed, in a first aspect, as a pharmaceutical composition for use in antineoplastic therapy, in mammals, including humans, comprising:

1. an alkylating anthracycline of formula Ia or Ib;



2. an antiviral compound, and a pharmaceutically acceptable carrier or excipient.

3. The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-acrididiny-4'-methanesulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis (2-chloroethyl)-4'-methanesulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drugs: Design, 1986, vol. 10, 441-453, and claimed respectively in US-A-4,318,118 and US-A-4,447,811. Both compounds interfere with DNA via the chlorophore and alkylate guanine at N7 position of DNA minor groove via their reactive sulfonyl group at 4' of the sugar moiety. Compounds Ia and Ib are able to overcome the resistance of all cells classes of cytotoxicity, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Antimetabolites are described in various scientific publications. The main representatives of this wide class of drugs are: the antifolates such as methotrexate, raltitrexed and trimetrexate ; the 5-fluoropyrimidine compounds such as 5-fluorouracil, floxuridine and capecitabine; the cytidine analogs like cytarabine, azacitidine and gemcitabine. See for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 432-450. The 5-fluoropyrimidine compounds and the cytidine analogs are the preferred antimetabolite compounds to be used in the present invention, more preferably 5-fluorouracil or gemcitabine. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, as combined preparation for simultaneous, separate or sequential use in antitumor therapy. A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, in amounts effective to produce a synergistic antineoplastic effect. The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antimetabolite compound as defined above and an alkylating anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergistic antineoplastic effect. By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a antimetabolite compound to mammals, including human.

By the term "administered" or "administering" as used herein, is meant parenteral and oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the compound with the antimetabolite compound activity, for example of the 5-fluoropyrimidine or cytidine class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according, inter alia, the particular formulation of the alkylating anthracycline of formula Ia or Ib being utilized, the particular formulation of the antimetabolite compound, such as one of the 5-fluoropyrimidine or cytidine class, being utilized, the particular tumor to be treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 300 mg/m² of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m² of body surface area.

In the method of the subject invention, for the administration of the antimetabolite compound the course of therapy generally employed is from about 1.1 to about 1.5 g/m² of body surface area. More preferably, the course therapy employed is from about 1 mg/m² to about 1 g/m² of body surface area. The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound in the prevention or treatment of metastasis or for the treatment of

tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis.

As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and an antimetabolite compound, such as a 5-fluoropyrimidine or cytidine derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and the antimetabolites and thus yields the most effective and least toxic treatment for tumors.

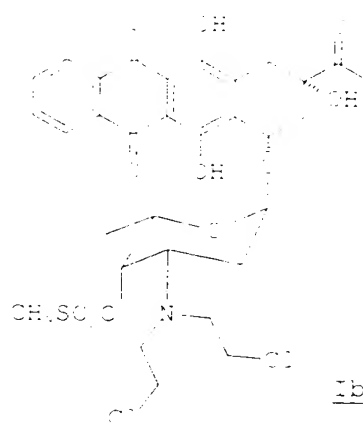
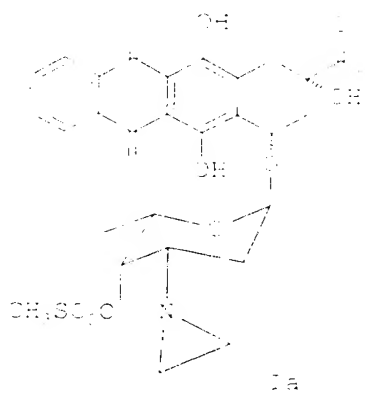
The superadditive actions of the combination preparation of the present invention may be shown for instance by in vivo tests for the antileukemic activity on disseminated L1210 murine leukemia. The combination of Ia with 5-Fluorouracil or gemcitabine, tested at the different doses and schedules, produces favorable ILS₅₀ values (Increase in life span:

[(median survival time of treated mice/median survival time of controls) x 100]-100), indicating a synergistic effect.

For these experiments Ia was solubilized in [Cremophora/EtOH = 6.5:3.5]/[normal saline]=20/80 v/v, while standard pharmaceutical preparation were used for the antimetabolite compounds.

Claims

1. A product containing an alkylating anthracycline of formula Ia or Ib:



and an antimetabolite compound as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. A product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin.

3. A product according to claim 1 or 2 wherein the antimetabolite compound is a cytidine analog.

4. A product according to claim 1 or 2 wherein the antimetabolite compound is a 5-fluoropyrimidine.

5. A product according to claim 3 wherein the cytidine analog is gemcitabine.

6. A product according to claim 4 wherein the 5-fluoropyrimidine is 5-fluorouracil.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound.

8. A composition according to claim 7 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the treatment of tumors.
10. Use according to claim 8 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.
11. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

ABSTRACT

Antitumor Synergetic Composition

- 5 The combined use of 4-demethoxy-1'-deamino-1'-acridinyl-4'-methanesulfonyl daunorubicin or 4-demethoxy-N,N-bis (2-methoxyethyl)-4'-methanesulfonyl daunorubicin and an anti-metastatic compound in the treatment of tumors, especially in the treatment or prevention of metastasis
- 10 in the treatment of tumors by the inhibition of angiogenesis.

